REMARKS

Claims 1-24 were pending in the application. Claims 11-19 and 21-24 have been cancelled, without prejudice, as being directed to a non-elected invention. Claim 3 has also been cancelled without prejudice, claims 1, 2, 4-7 and 20 have been amended, and new claims 25-31 have been added. Accordingly, after the amendments presented herein have been entered, claims 1, 2, 4-10, 20 and 25-31 will remain pending. For the Examiner's convenience all of the pending claims are set forth herein in Appendix A.

Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed. Specifically, support for new claims 25-27 can be found at page 2, lines 14-15 of the specification; support for new claim 28 can be found at page 3, lines 1-3 of the specification; support for new claim 29 can be found at page 5, lines 10-14 of the specification; and support for new claims 30 and 31 can be found at page 3, lines 3-7 of the specification.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objections to the Specification

The Examiner has objected to the specification and has required that Applicant "update the status (pending, allowed, *etc.*) of all parent priority applications in the first line of the specification."

Applicants respectfully submit that in view of the amendments to the specification presented herein, the foregoing objection has been rendered moot. Accordingly, the Examiner is required to reconsider and withdraw the foregoing objection to the specification.

Objection to the Drawings

The Examiner has objected to the drawings and has requested correction of the same based on the Notice of Draftsperson's Review attached to the instant Office Action.

Applicants note the Examiner's objection and respectfully submit that formal drawings in compliance with 37 C.F.R. § 1.84 will be submitted prior to the issuance of the present application.

Rejection of Claims 1-10 and 20 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-10 and 20 under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "the specification, *while being enabling for an isolated polypeptide comprising SEQ ID NO:2 encoded by the nucleic acid sequence set forth in SEQ ID NO: 1 or 3*, does not reasonably provide enablement for an isolated polypeptide or an isolated nucleic acid molecule that is at least 62% or 72% homologues to SEQ ID NO: 1, 2 or 3." (*Emphasis added*). In particular, the Examiner is of the opinion that

> [t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required, are summarized in *Exparte* Forman, 230 USPQ 546 (BPAI1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. The claims are drawn to an isolated polynucleotide encoding a polypeptide of SEQ ID NO:2 or an isolated polynucleotide encoding a polypeptide which is at least 62% identical to the amino acid sequence in of SEQ ID NO:2. This includes a whole universe of polypeptides with 62% identity to SEQ ID NO:2. The claims are drawn to an isolated nucleic acid comprising SEQ ID NO:1 or 3 or complement thereof, it is not clear if the complement is a full length complement or if this includes small fragments. The specification included isolated nucleic acid to encompass insertion deletion or substitution (see page 20, lines 14-31), isolated nucleic acids include fragments of 15 nucleotides in length (page 19, lines 1-5) and nucleic acids includes naturally occurring allelic variants (page 18, lines 24-30). The specification does not prove a measurable biological activity for the nucleic acid molecule, which would define the function of the molecule.

The Examiner is further of the opinion that

> [o]ne cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any polynucleotide fragment, which encodes a polypeptide fragment with sequence homology to SEQ ID NO: 2 without any biological properties associated with the homologue. Claims drawn to an isolated nucleic acid molecule, which encodes a protein and mutations within the nucleic acid molecule, which may effect the amino acid sequence. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al, Journal of Cell Bio. 111:2129-2138,1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar *et al.* Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie *et al.* Science, 247:1306-1310,1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all nucleic acid fragments with sequence similarity to the amino acid sequence shown in SEQ ID NO:2. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed, which include variation in the nucleic acid sequence resulting in changes in the encoded protein sequence.

To begin with, Applicants respectfully submit that the Examiner has indicated that the specification is enabling for an isolated polypeptide comprising SEQ ID NO:2 encoded by the nucleic acid sequences set forth in SEQ ID NOs:1 or 3 (see *supra*). Thus, Applicants respectfully submit that claims 1, 2 and 25-28 are enabled by the instant specification and respectfully request

that the Examiner withdraw this rejection as it pertains to claims 1, 2, 25-28 and claims depending therefrom.

With respect to claims 4 and 29-31 and claims depending therefrom, Applicants respectfully traverse the foregoing rejection on the grounds that, based on the teachings in Applicants' specification, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation. In particular, Applicants would like to bring to the Examiner's attention Example 14 of the *Revised Interim Written Description Guidelines Training Materials*. This Example provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity." The Guidelines also provide that "***[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.***" (***Emphasis added***).

Similarly, in the present case, claims 4 and 29-31 are directed to nucleic acid molecules that are 90-95% identical to SEQ ID NOs:1 or 3 or to nucleic acid molecules encoding polypeptides that are 90-95% identical to SEQ ID NO:2, wherein elevated levels of said nucleic acid molecules or polypeptides are indicative of a malignancy. Applicants have disclosed in the instant specification assays for identifying all of the at least 90% or 95% identical variants of SEQ ID NOs:1 or 3 or SEQ ID NO:4 whose elevated levels are indicative of a malignancy (see,

for example, pages 17, lines 23-30 and page 27, line 25 through page 29, line 5 of the specification).

In summary, it is Applicants' position that, given the guidance in the specification and the teachings in the art at the time the invention was made, one of ordinary skill in the art would be able to practice the invention as claimed using no more than routine experimentation. As the court held in *In re Wands*, a reasonable amount of experimentation is permitted to practice a claimed invention. The Court stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands,* 858 F.2d 731; 8 U.S.P.Q.2D (BNA) 1400, (CAFC 1988). Accordingly, based on the amendments to the claims and the comments set forth above, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 1-10 and 20 Under 35 U.S.C. §112, First Paragraph

The Examiner has also rejected claims 1-10 and 20 under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> [t]he written description in this case only sets forth SEQ ID NO: 1, 2 and 3 and therefore the written description is not commensurate in scope with the claims which read on allelic variants of SEQ ID NO:2. *Vas-Cath Inc. V. Mahurkar,* 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description inquiry, *whatever is now claimed."* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *(See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35

USC 112 is severable from its enablement provision (see page 115). What are allelic variants? Alleles are one of two or more alternative forms of a gene occupying the same locus on a particular chromosome and differing from other alleles of that locus at one or more mutational sites, which therefore encode allelic variant proteins, thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and or encoded variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel, 25* USPQ 2d 1601 at 1606 (CAFC 1993) *and Amgen Inc. V. Chugai Pharmaceutical Co. Its.,* 18 USPQ2d 1016. Furthermore, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement, which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(l), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". The specification included isolated nucleic acid to encompass insertion deletion or substitution (see page 20, lines 14-31), isolated nucleic acid molecules include fragments of 15 nucleotides in length (page 19, lines 1-5) and nucleic acids includes naturally occurring allelic variants (page 18, lines 24-30). However, no disclosure, beyond the mere mention of biologically active fragments (*i.e.* variants) is made in the specification. This is insufficient to support the generic claims as provided by the Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1 111. Therefore, only a nucleic acid sequence of SEQ ID NO: 1 or 3 encoding the polypeptide sequence of SEQ ID NO:2 meets the written description provision of 35 USC 112, first paragraph.

Applicants respectfully traverse the foregoing rejection on the grounds that there is sufficient written description in Applicants' specification regarding variants of the nucleic acid molecules and polypeptides of the invention to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. 2163.02).

As indicated above, Example 14 of the *Revised Interim Written Description Guidelines Training Materials* provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rational behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity."

Similarly, in the present case, claims 4 and 29-31 are directed to nucleic acid molecules that are 90-95% identical to SEQ ID NOs:1 or 3 or to nucleic acid molecules encoding polypeptides that are 90-95% identical to SEQ ID NO:2, wherein elevated levels of said nucleic acid molecules or polypeptides are indicative of a malignancy. Applicants have disclosed in the instant specification assays for identifying all of the at least 90% or 95% identical variants of SEQ ID NOs:1 or 3 or SEQ ID NO:4 whose elevated levels are indicative of a malignancy (see, for example, pages 17, lines 23-30 and page 27, line 25 through page 29, line 5 of the specification). Thus, based on the teachings in Applicants' specification, one of skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing.

In view of the foregoing, Applicants respectfully submit that the instant specification satisfies the requirements of 35 U.S.C. §112, first paragraph for written description and, accordingly, respectfully request that the Examiner reconsider and withdraw this rejection.

SUMMARY

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Dated: August 20, 2003

Respectfully submitted,

By _____

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APPENDIX A

1. **(Amended)** An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:1 or a complement thereof.

2. **(Amended)** An isolated nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2, or a complement thereof.

4. **(Amended)** An isolated nucleic acid molecule comprising a nucleotide sequence which is at least about 90% homologous to the nucleotide sequence of SEQ ID NO:1 or 3, wherein elevated levels of said nucleic acid molecule are indicative of a malignancy or a complement thereof.

5. **(Amended)** An isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of any one of claims 1, 2, 4, 25, 26, 27, 28, 29, 30 or 31 under stringent conditions.

6. **(Amended)** An isolated nucleic acid molecule comprising the nucleic acid molecule of any one of claims 1, 2, 4, 25, 26, 27, 28, 29, 30 or 31 and a nucleotide sequence encoding a heterologous polypeptide.

7. **(Amended)** A vector comprising the nucleic acid molecule of any one of claims 1, 2, 4, 25, 26, 27, 28, 29, 30 or 31.

8. The vector of claim 7, which is an expression vector.

9. A host cell transfected with the expression vector of claim 8.

10. A method of producing a polypeptide comprising culturing the host cell of claim 9 in an appropriate culture medium to, thereby, produce the polypeptide.

20. **(Amended)** A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of any one of claims 1, 2, 4, 25, 26, 27, 28, 29, 30 or 31 and instructions for use.

25. **(New)** An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:3 or a complement thereof.

26. **(New)** An isolated nucleic acid molecule consisting of the nucleotide sequence set forth in SEQ ID NO:1 or a complement thereof.

27. **(New)** An isolated nucleic acid molecule consisting of the nucleotide sequence set forth in SEQ ID NO:3 or a complement thereof.

28. **(New)** An isolated nucleic acid molecule which encodes a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, or a complement thereof.

29. **(New)** An isolated nucleic acid molecule comprising a nucleotide sequence which is at least about 95% homologous to the nucleotide sequence of SEQ ID NO:1 or 3, wherein elevated levels of said nucleic acid molecule are indicative of a malignancy, or a complement thereof.

30. **(New)** A nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence at least about 90% homologous to the amino acid sequence of SEQ ID NO:2, wherein elevated levels of said polypeptide are indicative of a malignancy, or a complement thereof.

31. **(New)** A nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence at least about 95% homologous to the amino acid sequence of SEQ ID NO:2, wherein elevated levels of said polypeptide are indicative of a malignancy, or a complement thereof.